

2.2 Mechanism of Action of Quinolones

Quinolones are a group of synthetic antibiotics obtained during chloroquine synthesis, which were discovered more than five decades ago (Leshner et al. 1962). The first member of the family, nalidixic acid, was soon introduced into clinics, but just for treating urinary infections by Gram-negative microorganisms (Deitz et al. 1963). In the next decade there was a constant release into clinics of novel quinolones such as the oxolinic acid. However the range of infections for which these antimicrobial compounds were useful remained to be quite limited. In the decade of the 1980s, a new generation of quinolones that contain a fluorine and novel ring moieties (fluoroquinolones) was developed (Ball 2000). This second generation of quinolones presented better pharmacological properties as well as a better entrance into Gram-positive microorganisms. Consequently, they were considered broad-spectrum antibiotics. Among them, ciprofloxacin still remains as the antimicrobial of choice not only for treating a variety of infections, mainly those by Gram-negative organisms, but also for treating Gram-positive infections. A newer generation of quinolones with improved pharmacological properties includes widely used antimicrobials such as levofloxacin (Anderson and Perry 2008).

The targets of the quinolones are the bacterial topoisomerases DNA gyrase and topoisomerase IV (Khodursky and Cozzarelli 1998; Shen et al. 1989). Both enzymes comprise two different subunits that form a tetramer and play essential roles in most processes of the DNA activity, including replication, transcription, recombination, and repair. While gyrase is the main responsible for modulating DNA supercoiling and removing the torsional stress associated with DNA replication and transcription, the role of topoisomerase IV in these processes is less relevant, being mainly involved in removing knots that accumulate in bacterial DNA as a result of different processes as well as in decatenating daughter chromosomes after replication (Champoux 2001; Levine et al. 1998). To perform their functions, bacterial topoisomerases generate double-strand breaks in the bacterial DNA. In such a way, while topoisomerases are essential for microbial life, their uncontrolled activity may cause fragmentation of the bacterial genome. Quinolones act by increasing the concentration of DNA–enzyme cleavage complexes and inhibit DNA ligation, hence increasing DNA breaks and stalling the replication fork progression (Anderson and Osheroff 2001). Thus, these antimicrobials have been dubbed as “topoisomerase poisons” because they convert these two enzymes into intracellular toxins (Kreuzer and Cozzarelli 1979).

It is worth mentioning that due to this mechanism of action that leads to DNA damage, quinolones induce SOS response and increase recombination and mutagenesis (Lopez et al. 2007; Lopez and Blazquez 2009; Phillips et al. 1987; Ysern et al. 1990). Therefore quinolones have been considered as promoters of genetic variation (Blazquez et al. 2012), including those processes leading to antibiotic resistance.